Aspects of Insulin Treatment

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This is the second of a series of articles based on presentations at the American Diabetes Association Scientific Sessions held 5–9 June 2009 in New Orleans, Louisiana, pertaining to insulin treatment approaches. At a symposium on aspects of continuous subcutaneous insulin infusion (CSII) treatment, Nancy Bohanon (San Francisco, CA) discussed new approaches to make this treatment available for subjects with type 2 diabetes and pointed out that "the pumps work!" She predicted that several of these products might be available within the next year.

Patch pumps

The Valeritas h-Patch technology has been used to develop a V-Go insulin patch pump (www.valeritas.com) to deliver both basal and bolus insulin, requiring a fixed basal dose, which appears to be preset to rates of 20, 30, and 40 units per 24 h. For bolus delivery, each click delivers 2 units up to a total of 36 units per 24 h. The pump is worn for 24 h, filled with an external device, with the backing removed to adhere to the skin. A button on the pump is pressed to insert a 30G needle. Bolus doses are delivered by pressing a button on one side that releases a bolus delivery deployment button—a safety feature to prevent accidental bolus delivery. After 24 h, a button is pressed to withdraw the needle. The device is purely mechanical, does not require a battery-driven pump or external controller, fits under clothing, and can be operated through clothing. In a user-preference program, patients liked it and considered it to be easy to use, discrete, and comfortable, although the filling mechanism was not considered to be ideal. Common to a number of these devices, although presumably allowing a less complex delivery mechanism, the single preset basal rate is somewhat disadvantageous, as an important benefit of CSII basal rates is the ability to deliver more and less insulin during periods of lesser and greater insulin sensitivity, given the exaggerated diurnal rhythm of insulin sensitivity characteristic of many type 2 diabetic patients. A report of use of the V-Go for 7 days in six patients previously receiving insulin glargine showed comparable glycemic control with significantly lower levels at bedtime and 3:00 A.M. (1).

Finesse (Calibra Medical) is another mechanical (nonelectrical) pump, with a reservoir containing up to 200 units, designed with two buttons, one on each side, with a double "squeeze" providing a fixed dose; different models deliver ½, 1, 2, or 5 units per squeeze. The unit is thin, with an external disposable cannula. It adheres to the body and can be operated through clothing, lasting up to 3 days. Although the device does not deliver basal insulin, given the lack of adjustable basal doses in the other devices, this may not be a complete negative, and it can be used to deliver bolus insulin or pramlintide—another potential advantage.

The Medingo Solo patch pump is electronic with a matchbox size patch and an external electronic controller, but it also has a button on the patch allowing boluses to be delivered manually. This is a full-featured insulin pump, with variable basal rates, allowing delivery of boluses in standard, dual-wave, and square-wave forms. The MedSolve Technologies Freehand pump is designed for use in subjects with both type 1 and type 2 diabetes; it is considerably smaller than currently available devices, with a remote controller, allowing multiple basal rates as well as delivering small bolus increments. Other very small insulin pumps in development are an insulin pump from Cellnovo, a Welsh company using microfluidics for insulin delivery; a patch pump from Starbridge Systems; the NiliMEDIX single-use disposable pump, which may incorporate a continuous glucose monitoring (CGM) sensor; and the STMicroelectronics and Debiotech insulin nanopump using a patch system and a separate electronic controller, smaller than traditional pumps and with a large insulin reservoir. Medtronic also may be developing a patch delivery system, controlled both with a remote unit and with manual bolus delivery by buttons on the device.

Another approach to basal insulin delivery being developed by Altea Therapeutics is the PassPort transdermal insulin patch, lasting either 12 or 24 h to provide constant basal insulin. This company is also developing a transdermal exenatide preparation, and devices are being developed for delivery of glucagon-like peptide-1 and pramlintide as well as insulin.

Approaches to CSII

Chris Sadler (La Jolla, CA) gave an update on CSII technology, emphasizing "convergence [and] connectivity with other devices" and new design aspects of existing and planned pumps from Animas, Insulet, Roche, and Medtronic. These devices may allow more precise and physiological insulin delivery, decreased glucose fluctuations and variability, lower risk of hypoglycemia, particularly during the night, and greater ability to handle dawn phenomenon and stress periods of increased insulin requirement. The devices also use "smart features" to eliminate stacking where insulin doses are administered without taking into account residual insulin delivered in previous boluses.

Ease of use features in the newer devices will include reminders to check glucose levels, to change infusion sets, and to alarm for low insulin reservoir content. Other important features of new pumps will be improved screens with higher graphic resolution, allowing easier programming; more comfortable infusion sets, allowing oblique and perpendicular insertions; and quick-release infusion sets to shower, swim, or change clothing. Auto-inserters being developed will allow more rapid and accurate insertion without crimping of the cannula and reducing "needle phobia" for children. Tactile feedback after delivery of insulin boluses and external controllers that allow pumps, particularly the "tubeless" patch pumps, to stay hidden will further improve ease of use.

Physiological features of CSII include multiple basal rates, as low as 0.025 units/h, particularly important in pediat-

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rics and for very insulin-sensitive adults, square and combination bolus features, and the calculation of suggested bolus based on glucose, insulin-carbohydrate ratios, glucose correction factors, duration of insulin action factors, and occlusion and safety alarms. Sadler pointed out that it is possible, unfortunately, to "outsmart a smart pump" and that patients need to use the bolus calculators to fully benefit from these devices, so that they do not become just "a fancy syringe." To use pumps properly, then, patients must regularly test glucose levels and must accurately estimate carbohydrate amounts. As pumps cannot anticipate exercise, meals, and stresses, it is useful for patients using the devices to understand the use of temporary basal and square- or dual-wave features and "to plan ahead." A further important concept is the need to adjust insulin treatment prospectively rather than falling into the trap of "reacting to numbers" with frequent between-meal corrections and such continual adjustment of basal rates that it is difficult to determine actual requirements. Clearly, to optimally use the devices, patients (and their health care professionals) need to regularly download and review glucose data. Pumps capture a wealth of data, and it is important to organize the information to allow rapid interpretation, with the "modal day" display particularly useful. Data analysis with artificial intelligence software should be designed to recognize glucose patterns and alert patients and providers to possible need for changes in basal or bolus doses, ideally with simplified and more rapid data downloading. Sadler noted that these approaches are leading to "stepwise progress to finally clos[e] the loop."

Connectivity is another important feature for coming CSII technologies. In addition to the transmission of CGM and control of insulin infusion rates by small devices, Sleep Sentry devices with remote display and alarms are being developed, and a very interesting concept will be of future connectivity to smartphones as data integrators. A service under development at Diasend.com promises to use cell phone technology and allow uploading of information from multiple meters, from CGM, and from pump insulin dose information to be shared by patients and clinicians. Modified smartphones with built-in glucose testing and pump controllers are also being developed. Future directions will include what Sadler termed "cool factors," such as colored and personalized pump controllers displaying "skins" to allow patients to upload images. Pumps are being developed with more intuitive interfaces and screens, perhaps made using flexible polymer devices including a flat, flexible rechargeable battery allowing the pump to conform to body shape, with low-power screens, longer battery life, and color-coding of CGM displays to rapidly inform the wearer whether blood glucose levels are stable, rising, or falling. The Charmr and Tolea insulin pump concepts embody some of these ideas. New infusion-sensor combinations may allow simultaneous continuous glucose measurement and infusion of insulin along with pramlintide and glucagon.

None of these approaches are easy for diabetic patients. Insulin still is slow-acting, there are still infusion site failures and overused sites, and there is a huge stress of constant need for troubleshooting, sensors not working, the need to wear multiple devices and carry back-up supplies, leading for some patients to an overwhelming psychological burden. There is also a burden for clinicians, and Sandler touched on the question, "How do we get paid?" Reimbursement for providers involved in these time-consuming treatment approaches may not be readily available.

Closing the loop

Bruce Buckingham (Stanford, CA) discussed approaches to "closing the loop" with CSII, a continuous glucose sensor, and a control program. "Why," he asked, "aren't we using closed loops today?" Issues include the time delay of existing glucose sensors, probably physiologically 6–7 min, but increased to 10–11 min due to the filters in the devices, as well as the accuracy of sensor glucose measurement. There is biological variability in insulin action and meal absorption, with insulin action after a subcutaneous insulin pump bolus taking at least 30 min to begin to affect glucose levels, "so you're at least a half hour behind the curve," although more rapidly acting insulin preparations, microneedles, local warming, hyaluronidase, and intraperitoneal pumps may improve this. Exercise is an extremely important factor, but it has proven difficult to determine appropriate dose change recommendations to address this.

The use of the Biostator beginning in 1976 led to interest in the development of technologies that would make this degree of precise glucose control available in convenient, portable devices; implanted pump studies have been carried out in France by Renard and colleagues over the past 2 decades furthering interest in such approaches (2). Basal glucose control is definitely achievable; Buckingham reviewed a study of 10 adults who were using a subcutaneous pump with an algorithm-based insulin controller, targeting a 120 mg/dl blood glucose, and who achieved mean fasting glucose of 125 mg/dl, with modest advantages in overnight glycemic stability over standard insulin infusion protocols, although not avoiding postmeal hyperglycemia (3). Another algorithm is the "moving horizon concept," which uses archived measurements to plan stepped insulin boluses, presumably acquiring information in this fashion about changes in the individual's insulin sensitivity. The most difficult aspect of closed loop insulin delivery is the meal bolus. Buckingham reviewed the simple observation that giving meal boluses 20 min prior to food ingestion leads to much flatter glycemic responses. In a study comparing closed loop with hybrid control, giving bolus doses ahead of the meal decreased postmeal peaks by ~30 mg/dl (4). This is of particular importance as closed loop systems are hampered by the time delay inherent in subcutaneous insulin administration. In the closed loop study, the mean glucose was 138 mg/dl, with 85% of glucose levels in target range (vs. 58% for the standard treatment approach). Another aspect of true artificial pancreas systems in mimicking physiological insulin patterns must be meal size and composition estimation. Glucose rates of change vary considerably with different meal compositions, with the most rapid changes after high-carbohydrate meals. Buckingham noted that CGM analysis programs can be modified to detect presumed meal-related increases in glucose levels brought about by omission of preprandial bolus dosing, which could be quite useful in pediatrics to then deliver insulin. "There's an explosion of studies being done," he commented, to detect the onset of eating and to detect failure of either the sensor or the insulin infusion system. Addressing physical activity is another issue, with a study using the Actical multidirectional piezoelectric accelerometer to measure activity suggesting an approach in modifying insulin sensitivity. This can be more simply accomplished with a heart rate monitor to judge changes in activity, and studies suggest this to be potentially useful as well.

Other studies aim to determine which of the sensors give optimal results and whether more than one sensor should be used at one time. Buckingham observed that fluorescent sensors appear to be an interesting approach. Further modifications of the artificial pancreas might be the use of glucagon to provide a brake to prevent hypoglycemia, an approach to bihormonal control that has been investigated in a porcine model (5), or the use of pramlintide to delay gastric emptying. Buckingham suggested that an approach to the design of algorithms may be to use "in-silico" computer modeling of type 1 diabetes rather than doing animal studies to allow development of approaches that would reduce glycemic variation in human studies and, ultimately, in patient treatment.

Table 1—*Controlled trials of CSII for type 2 diabetes*

Reference	Number of patients	Benefit of pump
7	20 randomized to MDI vs. CSII	3/10 achieved goal GHb with MDI, 8/10 with CSII (significant difference)
8	132 randomized to MDI (aspart/NPH insulin) vs. CSII	A1C 8.2→7.6% pump, 8→7.5% MDI (not a significant difference); lower am postmeal glucose with CSII, trend at other meals, 93% preferred pump
9	53 CSII vs. 54 MDI for 52 weeks	A1C 8.4→6.6% with MDI vs. 8.1→6.4% with CSII (not a significant difference)
10	17-person crossover trial (NPH insulin plus lispro three times daily vs. CSII)	A1C 9.0%, decreased to 8.6% with MDI and 7.7% with CSII (significant)
11	40-person crossover trial	No significant difference in A1C

CSII for type 2 diabetes

Bruce Bode (Atlanta, GA) discussed the use of insulin pumps for type 2 diabetes. There are, he stated, 5.6 million insulin-treated diabetic individuals in the U.S., of whom 4.5 million have type 2 diabetes. He cited estimates that 31% of type 1 but <5% of type 2 diabetic patients use CSII and that 71% of patients on multiple-dose insulin (MDI) regimens do not inject insulin outside the home, particularly those with type 2 diabetes. The goal of insulin treatment is, however, to duplicate physiology; Bode argued that an insulin pump is better than subcutaneous injections, particularly with the technology so rapidly changing to improve usability. CSII will, Bode stated, deliver better glycemic control and less hypoglycemia than NPH-based basal-bolus treatments, and although this has not been as clearly demonstrated as with analogs, pumps certainly offer an effective approach in reducing blood glucose, which Bode characterized as simple to administer and discrete. The promise of the patch pumps described by Bohanon is to further improve this approach to insulin administration for type 2 diabetes and to be cost effective, with comparable expense to that of current insulin analogs. For subjects requiring large insulin doses, U-500 insulin has been used successfully in pumps (6), although one should be careful of the potential for occlusion of the very concentrated insulin in the tubing. Medicare already reimburses use of current insulin pumps for subjects with A1C above goal, frequent hypoglycemia or hypoglycemia unawareness, the need for a flexible insulin regimen, and C-peptide and insulin autoimmunity requirements.

Bode reviewed a number of studies comparing insulin pump with MDI, which are summarized in Table 1 and certainly show feasibility of this approach, although not demonstrating superiority to MDI.

Bode concluded that insulin pump treatment "clearly improves glucose control with a simple regimen, improves quality of life and satisfaction, and may be the preferred therapy for type 2 [diabetic] patients not at goal." He suggested that randomized controlled trials of subjects failing to achieve control on MDI were needed to better understand which type 2 diabetic subjects are appropriate candidates for the approach, that ongoing ascertainment of cost-effectiveness will be important, and that the development of simple and easy-to-use pumps will be of great importance in allowing greater use of this technology.

A wide variety of approaches to CGM, pump insulin treatment, and subcutaneous insulin were presented at the meeting. A 16-week pilot study in which Bode participated was presented by Edelman et al. (abstract 428) describing 58 type 2 diabetic patients taken off oral medications other than metformin, placed on CSII beginning with a single basal dose, with 70% remaining on this and 18% controlled with two basal rates. Although not a controlled study, the observation that 57-year-old patients with duration of diabetes 13 years showed a reduction in A1C from 8.4 to 7.2% was of interest. Body weight increased on average by 1.9 kg, but there was no weight gain in those not previously on insulin, perhaps because 44% of them had received a thiazolidinedione. Hypoglycemia occurred in 59% of patients, although there were no severe episodes.

Studies of CSII

A number of further studies described approaches relevant to CSII. Heinemann et al. (abstract 230) infused insulin lispro with CSII at 0.5, 1.0, and 2.0 units/h for 4 h periods in 10 type 1 diabetic men and found that the glucose infusion rate required to maintain euglycemia increased progressively over each period. The researchers suggested that the typical maneuver of reducing basal insulin infusion rates often recommended for exercise or low glucose levels may not, then, rapidly lead to desired effects. Recognizing this prolonged effect of subcutaneous insulin delivered by CSII, Castle et al. (abstract 207) reported reduction in late postprandial hypoglycemia with automated low-dose glucagon delivery using a closed loop algorithm determining insulin and glucagon rates based on the difference between glucose and target level and the glucose rate of change. Russell et al. (abstract 235) similarly reported use of glucagon administration in reducing hypoglycemia in CSII, although they noted that subjects with prolonged duration of action of insulin lispro failed to show the effect with the algorithm used, suggesting that a change in model parameters might be required in such cases. Kovatchev et al. (abstract 228) studied a different approach to mitigate the time lags of CGM and subcutaneous insulin delivery, using model-predictive control algorithms and reporting a fivefold reduction in hypoglycemic incidents while increasing the time spent within the 3.9–7.8 mmol/l range.

Rodbard et al. (abstract 208) reported reduced frequency of hyperglycemia in

85 type 1 diabetic subjects viewing versus not viewing results of their CGM, and Jenkins et al. (abstract 209) showed that type 1 diabetic adults but not adolescents had improvement in A1C when initiated to CGM along with an algorithm guiding their responses, but not when the algorithm was begun 16 weeks after the beginning of CGM. Weinzimer et al. (abstract 211) reported that, with four visits and a follow-up telephone call over 6 months, type 1 diabetic subjects using CGM had a 0.2% reduction in A1C when monitoring at least 6 days weekly, but a 0.1% increase with less frequent monitoring. Raccah et al. (abstract 205) reported that type 1 diabetic subjects using combined CSII/CGM had a reduction in A1C from 9.4 to 8.3%, whereas those on CSII with conventional capillary glucose self-monitoring had a reduction in A1C from 9.3 to 8.7%. Hovorka et al. (abstract 206) found that during 88 overnight inpatient closed loop studies with an interacting multiple-model strategy to process glucose versus CSII alone in 17 type 1 diabetic youth and adults, hypoglycemia was reduced with 7 vs. 20% of overnight glucose levels <70 mg/dl, whereas time at target was increased with 66 vs. 38% of glucose levels 70–144 mg/dl.

Bragd et al. (abstract 229) reported that 15 CSII-treated type 1 diabetic patients randomized to glargine versus CSII had 0.3% lower A1C and 1.2 mmol/l lower mean CGM over 4 weeks with the latter, although glucose variability did not change; the nonblinded study protocol and prior CSII use may have influenced these results. Noh et al. (abstract 231) studied a 6-month period of CSII in 33 type 2 diabetic subjects with mean A1C 9.1% and reported reduction in A1C to 6.7%, with an 88% increase in endogenous insulin secretion (30-min change in insulin/change in glucose) and 43% reduction in the 120-min proinsulin-insulin ratio following a mixed meal; it is unlikely, however, that CSII per se was responsible for this improvement.

Prandial insulin treatment

Folkersen et al. (abstract 467) analyzed determinants of treatment effect of prandial insulin lispro versus basal insulin NPH or glargine in 594 subjects participating in the Hyperglycemia and its Effect after Acute myocardial infarction on caRdiovascular outcomes in patients with Type 2 diabetes (HEART2D) study, finding that those with lower baseline A1C were more likely to reach a level <7%, whereas those with higher baseline A1C were more likely to achieve an A1C reduction >0.3%; treatment group was not a significant predictor of glycemic change. Similarly, Riddle et al. (abstract 468) reported an analysis of 12 studies of 2,193 subjects treated by structured titration with insulin glargine and found that with baseline A1C <8, 8–8.4, 8.5–8.9, 9–9.4, and >9.5%, A1C decreased by progressively greater amounts of 0.9, 1.4, 1.6, 2.0, and 2.6%, but to progressively higher levels of 6.7, 6.8, 7.1, 7.2, and 7.6%, respectively. Further evidence of the importance of baseline glycemia was reported by Peters et al. (abstract 568) from a database of 181 type 2 diabetic subjects receiving insulin glargine with lispro three times daily before meals, 104 receiving glargine alone, and 196 and 448, respectively, receiving biphasic insulin lispro three times or twice daily. For all groups, lower A1C levels prior to the conclusion of the 16- to 24-week studies predicted the ability to achieve target levels <7%, interestingly with higher body weight also predicting success in glycemic control.

Cengiz et al. (abstract 19) performed euglycemic glucose clamps in seven type 1 diabetic youth after administering glargine and lispro insulin 0.4 and 0.2 units/kg body wt either as separate injections or mixed and found that mixing virtually abolished the lispro effect and should not be recommended.

Raman et al. (abstract 20) administered prandial insulin alone or at a 20% lower dosage with exenatide (1.25 or 2.5 μg) to eight type 1 diabetic adolescents prior to a standard breakfast and found ~90% reduction in glucose excursions over the subsequent 2 h, without glucagon suppression, but with delay in gastric emptying, suggesting that this agent may play a role in both types of diabetes. Karounos et al. (abstract 118) compared prandial administration of a rapid-acting insulin analog or pramlintide in 112 type 2 diabetic patients who were receiving basal insulin and reported 1.1 vs. 0.9% reduction in A1C, but 4.2 kg weight gain vs. 0.3 kg weight loss, with greater hypoglycemia frequency in the insulin-treated group. Those failing to achieve A1C <6.5% at 24 weeks were given both pramlintide or prandial insulin in combination, with little evidence of additional benefit over the succeeding 12 weeks.

Strojek et al. (abstract 546) treated 480 insulin-naïve subjects with biphasic insulin aspart before dinner versus insulin glargine at bedtime, both in combination with metformin and glimepiride, and demonstrated that A1C decreased from 8.5% to a significantly greater extent with biphasic insulin (by 1.4 vs. 1.3%), but that nocturnal hypoglycemia occurred 1.1 vs. 0.5 times yearly; weight increased 1.7 kg with both agents. Vora et al. (abstract 451) compared 310 type 2 diabetic patients receiving metformin plus either biphasic insulin aspart twice daily or insulin glargine once daily plus insulin glulisine three times daily before meals for 52 weeks and reported A1C reductions of 0.8 vs. 1.3%. Although the latter regimen was 27% more costly, principally because of the cost of more frequent capillary glucose monitoring, per unit A1C lowering there were cost savings of 23%.

Owens et al. (abstract 458) treated 135 type 2 diabetic subjects with insulin glargine and oral agents, titrating to fasting glucose <100 mg/dl. A total of 106 subjects failed to achieve A1C <7% at 3 months (mean 7.9%) and were randomized to addition of insulin glulisine prior to the main meal or to continuation of oral agents plus glargine alone, with the single prandial insulin dose leading to improvement in A1C and mean glucose without greater weight gain or more frequent hypoglycemia. Davidson et al. (abstract 496) presented information on a study of 343 subjects who failed to achieve adequate control with glargine plus orals after 14 weeks and who were randomized to addition of insulin glulisine before one, two, or all three meals for 24 weeks, reducing A1C from 7.9 to 7.4, 7.4, and 7.3%, respectively, with similar changes in body weight, although with a trend for more frequent hypoglycemia with the greater number of insulin doses. Rosenstock et al. (abstract 466) performed a similar study comparing 654 type 2 diabetic patients randomized to glargine plus Technosphere insulin for prandial control versus biphasic insulin aspart twice daily and found, however, A1C reductions of 0.6 vs. 0.7% over 52 weeks from baseline of 8.7%, although with 0.8 vs. 2.4 kg weight gain and with 48 vs. 69% mild-to-moderate and 4 vs. 10% severe hypoglycemia, respectively. Bergenstal et al. (abstract 478) randomized 565 glargine-treated type 1 diabetic patients to prandial administration of Technosphere insulin versus a rapid-acting insulin analog and reported 0.2 vs. 0.5% A1C reduction, but greater reduction in fasting and in 1-h postprandial glucose levels and 0.5 kg weight loss vs. 1.4 kg weight gain. Given its greater A1C reduction, it is not surprising that the injected analog was associated with a somewhat greater frequency of hypoglycemia.

Potocka et al. (abstract 232) compared Technosphere and Exubera inhaled insulin with insulin lispro prior to a standardized meal in 18 insulin-treated type 2 diabetic subjects and found that the nadir of endogenous glucose production occurred at 40, 130, and 75 min with the three preparations, suggesting the former to have potential benefit in reducing postprandial hyperglycemia, although total postprandial glucose excursion and suppression of glucose production were similar. Amin et al. (abstract 570) studied pulmonary function in 730 diabetic subjects receiving Technosphere insulin and 824 using other treatments. Mean levels of the forced expiratory volume in 1 s were significantly lower with the inhaled preparation, and there was a trend to lower pulmonary diffusing capacity. The investigators may be reducing evidence of adverse effect by giving mean levels of these parameters; the frequency of reduction in these parameters by, say, 25% or some other clinically relevant amount was not presented. Palermo et al. (abstract 233) showed that administration of 12 units of a buccal spray insulin (Generex Oral-lyn) reduced blood glucose levels following 75 g oral glucose in 15 subjects with impaired glucose tolerance. Geho et al. (abstract 424), Kidron et al. (abstract 434), and Iyer (abstract 442) described studies of orally administered insulin preparations in type 2 diabetic patients, showing effective glucose lowering.

Rys et al. (abstract 449) reported a meta-analysis of 12 trials of 3,553 diabetic subjects randomized to insulin aspart versus regular human insulin, showing a 0.1% reduction in A1C and reductions in glucose levels after breakfast, lunch, and dinner by 26, 20, and 15 mg/dl, respectively, with a one-third lower rate of nocturnal hypoglycemia. Heller et al. (abstract 505) reported a similar analysis of 10 trials of 3,727 diabetic subjects receiving NPH insulin with either regular human insulin or insulin aspart and confirmed the findings of 0.1% lower A1C, lower postprandial glucose levels, and reduction in nocturnal hypoglycemia. Boron et al. (abstract 513) randomized 180 hospitalized subjects treated with insulin glargine at bedtime to receive either human insulin or insulin glulisine three times daily before meals and reported 6, 7, and 13 mg/dl lower mean, preprandial, and postprandial glucose with glulisine, the difference increasing with duration of treatment, so that mean preprandial glucose levels averaged 160 vs. 131 mg/dl after 7 days. Hypoglycemia rates were similar. Arnolds et al. (abstract 528) performed euglycemic clamp studies in 12 nondiabetic subjects after administration of 0.2 units/kg of insulin aspart versus glulisine and found the glucose infusion during initial 30 min after administration to be approximately twice as great with the latter, although the time of maximal insulin effect was identical at 90 min with both products. Bolli et al. (abstract 555) randomized 37 obese type 2 diabetic subjects to 0.2 units/kg insulin aspart versus glulisine prior to a test meal, finding glucose peaks of 181 vs. 170 mg/dl.

Basal insulin treatment

Hohberg et al. (abstract 448) administered metformin with either NPH or glargine insulin endeavoring to obtain fasting glucose <100 mg/dl to 28 type 2 diabetic patients, showing that with fasting glucose reduced from 158 to 120 mg/dl, postprandial proinsulin release was similarly reduced with both insulin treatments, but glargine was more effective after the evening meal in reducing proinsulin levels. Liebl (abstract 524) treated 204 previously insulin-naïve type 2 diabetic patients receiving metformin and mealtime repaglinide with insulin detemir versus NPH, showing 1 kg weight loss versus 1 kg weight gain with reduction in systolic blood pressure and increase in HDL in the former group, although A1C reduction was similar at 1.8 vs 1.6% from baseline levels around 8.7%.

Fonseca et al. (abstract 23LB) analyzed a medication and diagnosis database for 10,667 versus 2,009 oral agent–treated type 2 diabetic subjects receiving glargine versus NPH insulin and found evidence of fewer microvascular events in the former group after adjusting for baseline differences in age, A1C, sex, and comorbidities. Lee et al. (abstract 576) compared the effect of adding glargine versus NPH insulin to oral agents in a combined analysis of four trials, comparing outcome in 1,690 subjects aged <65 and in 441 subjects aged >65, confirming a lower rate of nocturnal hypoglycemia in the older group, and also finding that A1C decreased 1.2% with glargine vs. 0.9% with NPH insulin in the older patients. Thibaudeau et al. (abstract 435) described studies with recombinant insulin covalently conjugated to Cys34 of recombinant human albumin, showing longer biological activity than insulin glargine in a diabetic rat model, suggesting that this form of insulin might require administration less often than once daily.

Dailey et al. (abstract 480) performed a meta-analysis of 20 studies of insulin glargine and 4 studies of insulin detemir. A1C decreased 1.4% with both agents, and weight increased 2.3 vs. 1.7 kg, an insignificant difference, although the administered insulin dose was significantly less with glargine at 37 vs. 52 units daily. Half of the detemir-treated patients required twice-daily dosing.

In innovative studies using CGM, improvement in glycemia was reported by Rong et al. (abstract 443) in insulin-treated diabetic patients who were administered acarbose and by Matsuura et al. (abstract 492) in patients who received detemir or glargine insulin monotherapy with addition of miglitol. Chun et al. (abstract 450) treated type 2 diabetic subjects with insulin glargine titrated to fasting glucose <120 mg/dl; 75 patients received a meglitinide plus α-glucosidase inhibitor, whereas 53 received glargine with a sulfonylurea plus metformin. A1C levels decreased from 8.9 to 8.0 vs. 8.5%, and despite similar premeal glucose of 116 vs. 128 mg/dl, mean postprandial glucose was 209 vs. 255 mg/dl, suggesting benefit of targeting postprandial glycemia.

Further studies of insulin treatment

Boothe et al. (abstract 5LB) produced recombinant human insulin from transgenic safflower plants and reported that insulin could be purified from the seeds and administered both in animals and in 23 healthy volunteers with bioequivalence to Humulin R. Kreugel et al. (abstract 440) randomized 130 obese insulin-treated diabetic subjects in a crossover trial with 5 mm × 31G needles vs. 8 mm × 31G needles and found similar A1C over 3 months and similar patient preference, without difference in hypoglycemic events, bruising, or pain. There was less bleeding with the shorter and less insulin leakage with the longer length needles.

Retnakaran et al. (abstract 494) treated 34 type 2 diabetic subjects with A1C 7% on zero to two oral agents with insulin detemir plus premeal aspart for 4–8 weeks, examining a 4-h meal test before and 1 day after the completion of the intensive treatment protocol. Twenty-three patients had fasting glucose <126 mg/dl before the meal test, with lower glucose and greater C-peptide levels through the meal test than those failing to achieve normal fasting glucose, suggesting that even with apparently adequate glycemic control there is clinically important glucose toxicity. Li et al. (abstract 499) randomized 382 newly diagnosed type 2 diabetic patients to intensive insulin treatment versus the sulfonylurea gliclazide, with or without metformin, with treatment stopped after 2 weeks of euglycemia, and reported that insulin treatment prolonged the time in glycemic remission.

Miller et al. (abstract 629) reported predictors of hypoglycemia in a nationally linked database of 1.38 million Veterans Administration diabetic patients followed from 2000 to 2004, with 2.02 million hypoglycemic episodes. Among those receiving insulin, hypoglycemia occurred 5.8- and 7.3-fold more often, respectively, with histories of prior hypoglycemia and of prior ketoacidosis or hyperglycemic coma, whereas in those not receiving insulin the respective risk increases were 10- and 14-fold greater. Other risk factors, associated with 1.1- to 1.4-fold increases in hypoglycemia in both treatment groups, were history of amputation, retinopathy, neuropathy, renal disease, peripheral arterial disease, and recent hospitalization.

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